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A Multivariable Risk Factor Analysis of the Portoenterostomy (Kasai) Procedure for Biliary Atresia

Twenty-Five Years of Experience From Two Centers

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Objective
The authors investigated risk factors for failure after portoenterostomy for biliary atresia using univariate and multivariable methods.

Summary Background Data
Kasai's portoenterostomy has gained worldwide acceptance as the initial surgical therapy for infants with biliary atresia. Although extended survival has been achieved for many patients, factors influencing outcome have not been defined clearly.

Methods
The authors analyzed risks for failure in 266 patients treated from 1972 to 1996 by the Kaplan–Meier product limit estimate and Cox proportional hazards model. Failure was defined as death or transplant.

Results
Age at surgery, surgical decade, and anatomy of atretic bile ducts were identified as independent risk factors. Five-year survival was 49% and median survival was 15 years when bile drainage was achieved. Sixty-five patients had liver transplants. Mean age at transplant was 5.4 years.

Conclusions
The outcome after portoenterostomy for biliary atresia is determined by age at surgery and anatomy of the atretic extrahepatic bile ducts. Liver transplant will salvage patients with failed Kasai with 10-year posttransplant survival of 71%.

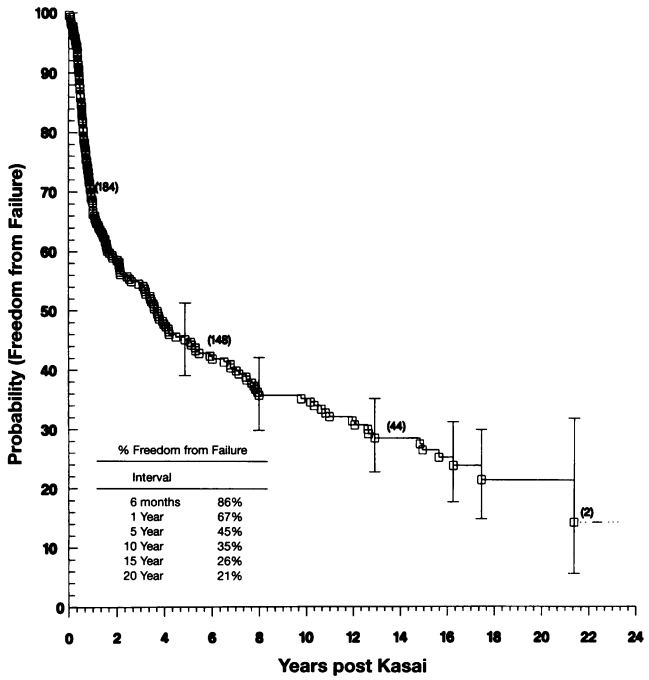

Figure 1. Freedom from failure post-Kasai for biliary atresia (1972–1996; n = 266). Failure was defined as death or transplant. The graph represents the total experience of 266 patients without consideration of any variables or whether bile drainage was achieved. The squares represent actual events, positioned along the horizontal axis at the time of the event and by the Kaplan–Meier method along the vertical axis. The vertical bars represent 95% confidence intervals.

Since Kasai described the portoenterostomy for infants with biliary atresia, the operation has been adopted throughout the world. This procedure has altered profoundly the prognosis for a disease that, before Kasai's operation, had been uniformly dismal. Although extended survival has been reported from many centers, factors affecting outcome have not been defined clearly. Inevitably, this has led to confusion and controversy. In an effort to identify those variables that influenced the surgical outcome, we carried out a multivariable risk factor analysis.

PATIENTS AND METHODS

From 1972 through 1996, 295 infants had surgical correction of extrahepatic biliary atresia. Long-term follow-up was possible for 266 patients, who constitute the basis for this study. The operations were performed in Washington DC/New York (RPA) or Denver, Colorado (JRL). All infants had the basic operation at the liver hilum described by Kasai.[1,2] Sixty patients had unmodified Roux-en-Y construction of the jejunal conduit. Modifications of the intestinal conduit, including external venting or incorporation of an intussuscepted valve into the conduit or both, were performed in 206 patients.

Merely accomplishing bile drainage after operation is not equivalent to success. We therefore defined our endpoint as "failure" or time to either death or transplant. We also analyzed survival in those patients having undergone liver transplant after Kasai procedure.

Statistical Analysis

The data were examined by means of standard contingency tables and the Kaplan–Meier product-limit estimate.[3] The Cox proportional hazard model[4] was used for multivariable analysis, estimating the relative risk of failure and 95% confidence intervals, adjusting for the other independent risk factors. Potential risk factors for failure included gender, age, race, surgical decade, associated anomalies (polysplenia), hepatic histology, atretic bile duct anatomy–histology, and type of operation (conduit reconstruction). Any possible institutional effects were corrected by stratification in the Cox model. Data were analyzed using SAS System software (SAS Institute, Inc, Cary, NC).

RESULTS

The cumulative results from the total experience with 266 patients are summarized in Figure 1. Freedom from failure was 86% at 6 months, falling to 21% at 20 years.

Table 1. INDEPENDENT RISK FACTORS FOR FAILURE POST KASAI (COX MODEL)

Variable	p	Risk Ratio	95% CI
Age at surgery*			
50–70 days	0.3805	1.195	0.80–1.78
>70 days	0.0077	1.690	1.15–2.48
Decade: 1970s	0.0001	1.916	1.42–2.59
Atretic duct anatomy†			
Type A (atretic ducts in continuity)	0.0037	1.791	1.21–2.65
Type C (discontinuous atretic ducts)	0.0312	2.175	1.07–4.41

CI = confidence interval.
* *vs.* 49 days old.
† *vs.* baseline type B (patent distal ducts).

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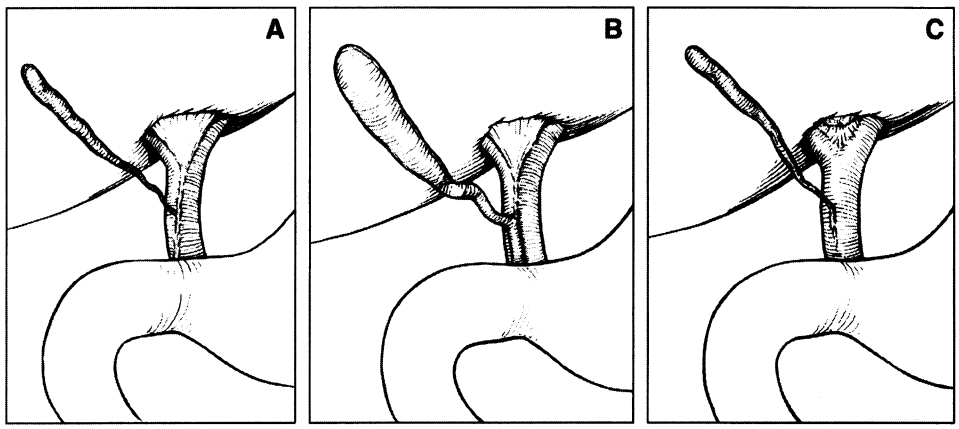

Figure 2. The anatomy of the atretic bile ducts found at time of operation (with some minor variation) can be characterized as (A) fibrotic extrahepatic bile ducts in continuity, (B) fibrotic proximal ducts, distal ductal patency, or (C) fibrotic gallbladder with absent or scanty remnants of the remaining ductal structures.

The Cox model confirmed that among the variables investigated, only age at surgery (p = 0.0077), surgical decade (p = 0.0001), and atretic bile duct anatomy (p = 0.0037) were independent risk factors (Table 1).

Significant Covariates

Age

Using the Cox model to analyze the relation between age at surgery and risk of failure, we stratified the patients into three groups: 0 to 49 days (<7 weeks), 50 to 70 days (7–10 weeks), and 71+ days (>10 weeks). The median age at surgery in this series was 62 days.

There was no increased risk of failure comparing the outcomes between the intermediate group (50–70 days) with those operated on before 49 days (p = 0.38). However, the older patients (71+ days) were at significantly higher risk of failure when compared to either of the other patient cohorts (p = 0.0077) (Table 1).

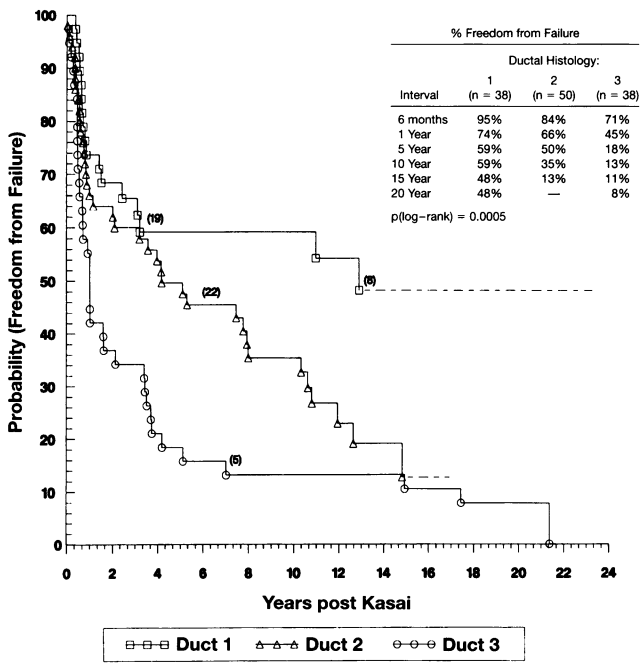

Figure 3. Freedom from failure post-Kasai for biliary atresia, stratified by ductal histology (1972–1996; n = 126). The ductular structures within the resected "cone" at the porta were measured and classified according to lumenal diameter. The squares, triangles, and circles represent actual events, positioned along the horizontal axis at the time of the event and by the Kaplan–Meier method along the vertical axis.

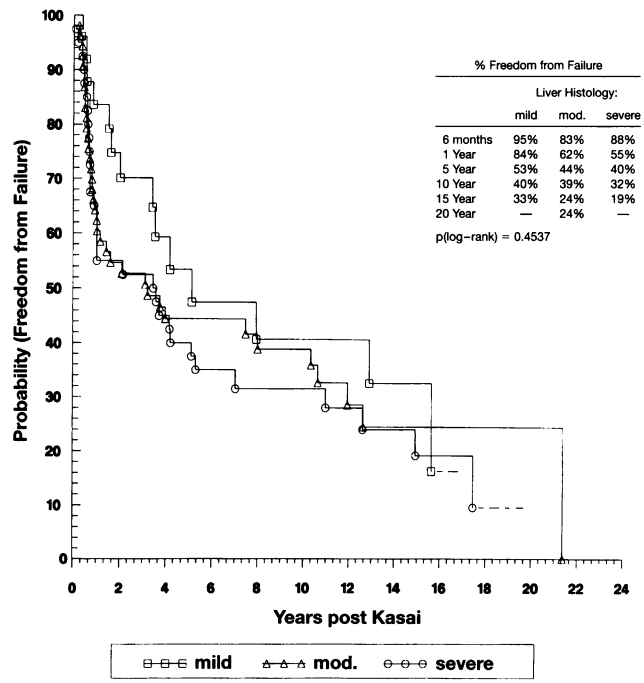

Figure 4. Freedom from failure post-Kasai for biliary atresia stratified by liver histology (1972–1996; n = 126). The liver histology from biopsy specimens obtained at the time of Kasai operation was graded as mild fibrosis, moderate fibrosis, or severe fibrosis (cirrhosis). The squares, triangles, and circles represent actual events, positioned along the horizontal axis at the time of the event and by the Kaplan–Meier method along the vertical axis.

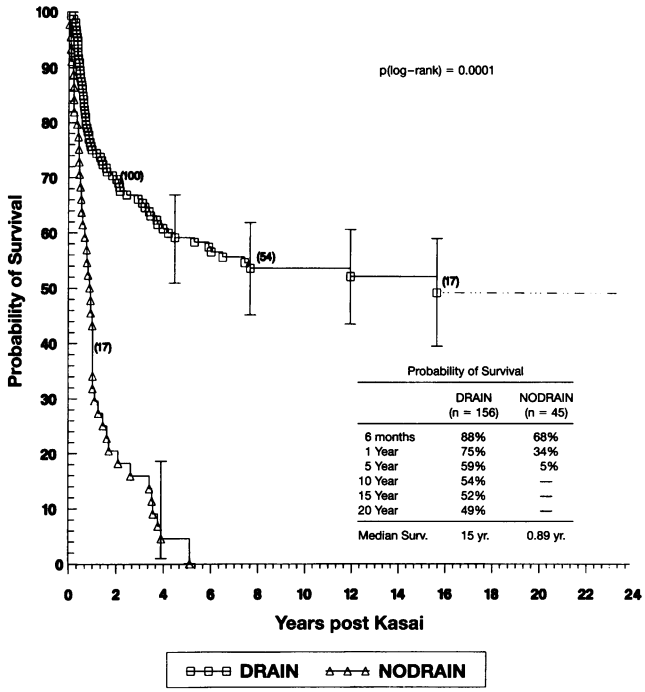

Figure 5. Survival post-Kasai (no transplant) (1972–1996; n = 201). The 20-year post-Kasai survival, when bile drainage was achieved, was 49%, and the median survival was 15 years. When the operation failed to result in bile drainage, survival was <1 year. The squares and triangles represent actual events, positioned along the horizontal axis at the time of the event and by the Kaplan–Meier method along the vertical axis. The vertical bars represent 95% confidence intervals.

Decade 1970s

Results of the Cox analysis indicated that after adjusting for all other covariates, patients having surgical correction in the decade of the 1970s had a higher risk of failure than those operated on subsequently (p = 0.0003) (Table 1). Among the factors undoubtedly influencing this result were the "learning curve" for the operation in the early years as well as the lack of mature strategies for managing complications, including cholangitis, portal hypertension, and nutritional deficiencies.

Anatomy of Atretic Bile Ducts

The anatomy of the atretic extrahepatic bile ducts was variable (Fig. 2). The most common finding was that of complete fibrous obliteration of an anatomically intact extrahepatic biliary duct system with all ducts in continuity (type A, n = 192). In 47 patients, the gallbladder, cystic duct, and common bile duct were patent to the duodenum, but the proximal ducts emerging from the liver in continuity with the distal system were fibrotic (type B). In 16 patients, the fibrotic gallbladder was discontinuous with the scanty remnants of ductal tissue, and a well-defined fibrous cone at the porta was lacking (type C).

Independent of the method of biliary reconstruction, the risk of failure in patients with either type A or type C ductal anatomy was higher when compared to patients with type B configuration. In patients with completely obliterated extrahepatic ducts in continuity (type A), the risk ratio was 1.7 (p = 0.0043), and for those with the discontinuous or absent extrahepatic ductal structures (type C), the risk ratio was 2 (p = 0.0441) (Table 1).

Histologic Analysis

Bile Duct

The findings from this study were consistent with those from previous reports.[5,6] We analyzed 126 patients (Washington, DC/New York) in whom the resected fibrous tissue at the porta showed patent biliary ductules >150 μm in diameter (type I) with those having smaller ductular structures (type II) or fibrous tissue devoid of biliary channels (type III) by univariate and multivariable methods. Both the results from the Kaplan–Meier estimate and the Cox model confirmed that ductal histology was a highly significant independent risk factor (p = 0.0002) (Fig. 3).

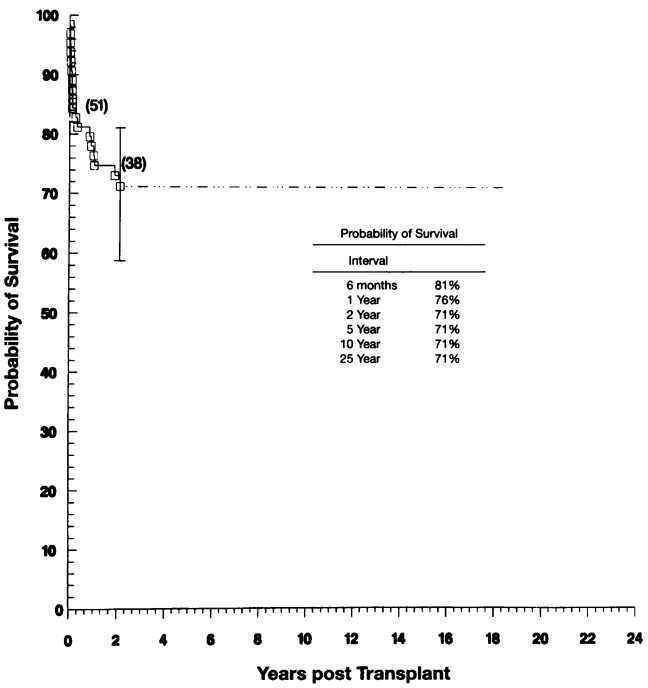

Figure 6. Biliary atresia, survival postliver transplant (1972–1996; n = 65). Sixty-five patients had liver transplant after Kasai operation. Median age at transplant was 5.4 years. Ten-year posttransplant survival was 71%. The squares represent actual events, positioned along the horizontal axis at the time of the event and by the Kaplan–Meier method along the vertical axis. The vertical bars represent 95% confidence intervals.

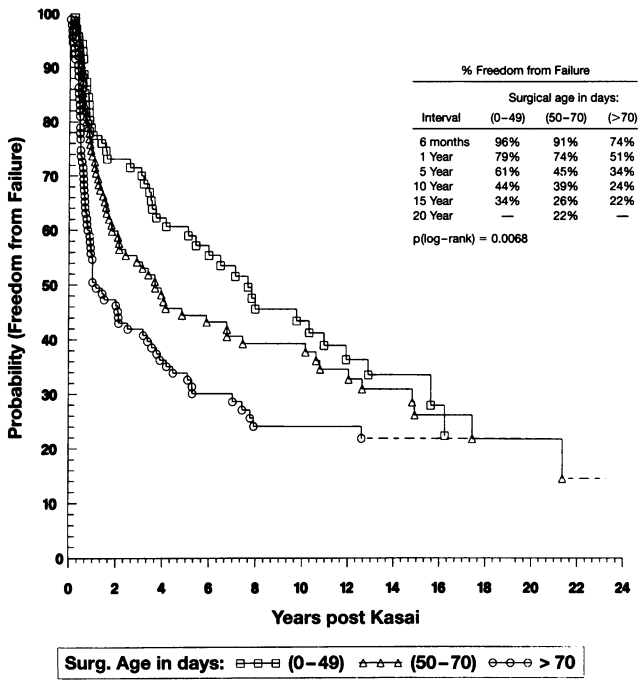

Figure 7. Freedom from failure post-Kasai for biliary atresia, stratified by age (1972–1996; n = 266). Patients were stratified according to age. As confirmed by the Cox model, those having Kasai procedure after 10 weeks (71+ days) had a significantly higher risk of failure when compared to those operated on before 7 weeks (49 days) (p = 0.0068). There was no additional risk for those between 7 and 10 weeks (50–70 days) compared to the <49 day group. The squares, triangles, and circles represent actual events, positioned along the horizontal axis at the time of the event and by the Kaplan–Meier method along the vertical axis.

Liver

It seemed intuitive that surgical outcome would correlate with hepatic histology. We compared outcomes from patients in whom the liver biopsy specimens obtained at the time of portoenterostomy showing pathologic changes consistent with either mild fibrosis, moderate fibrosis, or established cirrhosis and found that there was no added risk of failure between histologic groups. Thus, we conclude that hepatic histology was not an independent risk factor (Fig. 4).

Bile Drainage After Portoenterostomy

Patients having a Kasai operation without subsequent transplant (n = 201) were analyzed using the Kaplan–Meier product limit estimate. Survival at intervals from 6 months to 20 years comparing the bile drainage group (n = 156) with the nondrainage group (n = 45) is seen in Figure 5. Predictably, if bile drainage was not achieved after portoenterostomy, survival was unlikely. For patients in whom bile drainage was accomplished, the 20-year survival was 49% and the median survival, without liver transplant, was 15 years.

Liver Transplantation

Sixty-five patients eventually underwent liver transplantation. The mean age at transplant was 5.4 years (range, 0.59–21.5 years). The Kaplan–Meier 10-year posttransplant estimated survival was 71% (Fig. 6).

DISCUSSION

This study supports Kasai's initial observation that the age of the patient at the time of surgery influenced outcome.[2] Because many patients come to surgical attention at or about 7 weeks, it is particularly relevant that there was no observed increased risk of failure comparing patients having surgical correction between 7 to 10 weeks (50–70 days) with those operated on before age 7 weeks (<50 days). However, after age 10 weeks (71+ days), the risk of failure was increased significantly (Table 1, Fig. 7). This finding, whereas generally accepted, is somewhat at variance with conclusions from the King's College Hospital, London, experience in which the authors found that increasing age at operation did not adversely affect outcome.[7]

Inevitably, there will be operative failures or patients or both in whom liver disease progresses despite provision of bile drainage after the portoenterostomy. For these patients, only liver replacement offers hope for salvage.[8]

Azarow et al.[9] proposed that patients with biliary atresia could be selected for portoenterostomy based on the liver histology from a percutaneous biopsy. They contended that patients who will not benefit from Kasai's operation should be identified before surgery and preferentially referred for primary liver transplantation. Notwithstanding possible differences in pathologic interpretation of biopsies between institutions, the recommendation is inconsistent with the findings from this study because hepatic histology was not shown to be an independent risk factor for failure.

These authors acknowledge that there was no difference in posttransplant survival between patients transplanted primarily and those receiving a transplant after a failed Kasai,[10] an observation that has been confirmed in many transplant centers.[11–13] Further, even when the operative outcome met the criteria for failure (death or transplant), there often was significant palliation, with a 5-year survival of 49% and a median pretransplant survival of 5.4 years, whereas survival without drainage (and presumably without Kasai operation) was 0.89 year and the 5-year survival was nil.

The observation that anatomy and histology of the atretic ducts were risk factors for failure is consistent with the findings reported by Davenport and Howard,[14] who

also confirmed correlation between outcome and the characteristics of the portal remnant. They described the fibrous portal remnants as scanty or atrophic or both in their older patients. Although we did not observe a correlation between the patients' age and the anatomy of the atretic bile ducts, we concur with their conclusion that the status of the biliary remnant has prognostic significance. Those authors even suggested that operative observations by an experienced surgeon may have predictive value, an attractive and probably valid speculation.

Previous enthusiasm for venting the biliary conduit externally has waned. Likewise, incorporation of an intussuscepted valve into the conduit, theoretically to prevent or inhibit reflux was not shown to impact on outcome. Whereas venting or valving may have minor or temporary influence on the incidence of cholangitis, omitting either was not associated with increased risk of failure. Ando et al.[15] and others[16] assessed liver function, incidence of infection, and rate of growth before and after stomal closure and reached a similar conclusion.

CONCLUSIONS

The following conclusions can be drawn:

1. The risk of failure after portoenterostomy for biliary atresia is related to age at operation and the anatomy and histology of the atretic extrahepatic bile ducts.
2. Neither the gender, race, liver histology, presence of associated anomalies, nor the type of conduit construction was an independent risk factor for failure.
3. If bile drainage was achieved by the portoenterostomy, the median survival without transplant was 15 years.
4. For patients ultimately requiring transplant, the portoenterostomy significantly extended pretransplant survival, with the median age at transplant 5.4 years.
5. The portoenterostomy and liver transplant operations are complementary, and liver transplantation will rescue patients with a failed Kasai with an estimated 10-year posttransplant survival of 71%.

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Discussion

DR. ARNOLD G. CORAN (Ann Arbor, Michigan): I would like to congratulate Dr. Altman on what I think is a superb presentation and to thank him for providing me with the manuscript ahead of time. I think we were all privileged today to hear this presentation on biliary atresia, which I think is destined to become a landmark article on the subject.

Since Morio Kasai first introduced the concept of a portoenterostomy in the Japanese literature in 1959 and subsequently in the third volume of *The Journal of Pediatric Surgery* in 1968, many pediatric surgeons throughout the world, but especially in the United States, have questioned the efficacy of this operation in correcting biliary atresia. Today, Dr. Altman has presented unequivocal evidence that about one quarter of infants undergoing a portoenterostomy will be long-term survivors at 20 years. These data are identical to those presented a few years ago by Dr. Morio Kasai, in which there was also a 25% survival.

Dr. Altman's sophisticated and detailed analysis of his data has supported most of our current concepts regarding prognostic factors that impact on the success of the portoenterostomy, such as age at operation, bile duct histology, decade of operation, and postoperative bile drainage. However, a lack of correlation with liver histology is quite surprising to me, especially because most of the other series have found a close correlation between the presence of cirrhosis and poor long-term survival. Likewise, in our own smaller series, liver histology appeared to be a major factor in survival.